

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 December 2001 (27.12.2001)

PCT

(10) International Publication Number
WO 01/97817 A1

(51) International Patent Classification⁷: **A61K 31/70**,
38/18, 38/22, 38/28, 38/30, C07K 14/475, 14/60, 14/61,
14/62, 14/65

(21) International Application Number: PCT/US01/41080

(22) International Filing Date: 21 June 2001 (21.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/598,523 21 June 2000 (21.06.2000) US

(71) Applicants and

(72) Inventors: **LIU, James, Zhou** [US/US]; 462 Burns Drive
North, Westerville, OH 43081 (US). **ZHANG, Bao, Zhu**
[US/US]; 462 Burns Drive North, Westerville, OH 43081
(US).

(74) Agent: **SCOTNEY, Cheryl, S.**; Standley & Gilcrest LLP,
495 Metro Place South, Suite 210, Dublin, OH 43017 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HEALTH PROMOTING FOODS

(57) Abstract: A health promoting food composition of the present invention contains hormones having immune and intelligence enhancing effect, or those hormones in combination with anti-viral and/or anti-bacterial antibodies, and/or fructans. Thymic, adrenal and thyroid hormones are the main hormones in enhancing the immune function and in promoting intelligence development. The anti-viral antibodies are antibodies used against rotaviruses, respiratory syncynthial viruses, influenza viruses, and parainfluenza viruses. Fructans that may be used are oligofructoses and inulin. The health promoting food may be used to: (1) increase the immune function and enhance mental development of a mammal; (2) inhibit viral and/or bacterial infection in a mammal; and (3) selectively stimulate colon bifidobacteria and lactobacilli in a mammal. The combination of those hormones, fructans, and viral antibodies in a nutritional product may be used to provide overall health protection for a mammal. A method of production and use of the health-promoting food is also provided.



WO 01/97817 A1

HEALTH PROMOTING FOODS

FIELD OF THE INVENTION

5

The present invention relates to a method of production and use of health promoting foods. The present invention is to a method to fortify foods artificially with immune and intelligence enhancing hormones alone, and in combination with viral and bacterial antibodies and intestinal health promoting fructans. The health promoting foods include dietary supplements, infant formulas, nutritional products for aged people and for other people in need of those health promoting factors. The health promoting foods may also be used for feeding animals.

10

BACKGROUND AND SUMMARY OF THE INVENTION

15

Several hormones play critical roles in developing and maintaining immune function, in developing and maintaining intelligence ability. Thymic hormones, adrenal hormones, and thyroid hormones have been shown to contribute to the normal functions of human and animal immune systems, neuroendocrine systems, reproductive systems, and the central nervous systems. Currently, at least four separate thymic hormones have been isolated. They are thymosin, thymulin, thymopoietin, and thymic humoral factor. These hormones are produced in the thymus gland. The thymus gland is the primary lymphatic tissue located in the thorax behind the sternum. The thymus gland is large at birth but is less functional in producing hormones to enhance the maturation of lymphocytes later in life. To become mature, all T-lymphocytes must reside in the thymus gland for a period of time. The T-cell in the thymus gland is called a thymocyte and acquires either CD4 or CD8 characteristics. During the maturation period within the thymus gland, T-lymphocytes

20

25

eventually become either CD4 cells or CD8 cells. Only those thymocytes expressing CD4 or CD8 characteristics are positively selected to immigrate, by way of the thymus gland, to the peripheral lymphatic system to fight against foreign substances.

Therefore, without a functional thymus gland to produce the needed thymic hormones,

5 the body's immune system may not be fully functional. Researchers have also observed an important interaction between the thymus gland and the pituitary gland, which is located in the brain. The animal study showed that surgically removal of the pituitary gland resulted in a 50% reduction in both thymus gland weight and the concentration of thymosin. Additionally, age-related deterioration of learning and
10 memory abilities has been linked to the atrophy of the thymus gland. Currently, no infant formulas contain thymic hormones.

Adrenal hormone, dehydroepiandrosterone (DHEA) is produced from cholesterol in the adrenal glands and serves a wide variety of functions, providing health and longevity benefits. It is a primary hormone that the body converts on
15 demand into such hormones as estrogen, progesterone, testosterone, and androstenedione. Blood concentration of DHEA is low in infants and young children. Numerous studies have demonstrated that DHEA is needed for reducing incidence of infectious diseases in infants and young children, as well as in other aged people. Currently, no infant formulas contain DHEA.

20 Thyroid hormone is needed for proper development of normal brain and neural tissue in early life. It has been reported that thyroid diseases affect approximately 5% of the world's population, and that all ages may be affected. Hypothyroidism in the young child, particularly the neonate, is truly an urgent situation. Because proper development of normal brain and neural tissue in early life requires adequate levels of
25 thyroid hormone, deficiency may cause severe, irreversible mental and physical

handicaps, a condition known as cretinism. It is known that the major part of brain development, about 90%, occurs during the first 2 years of life. The longer the child with hypothyroidism remains untreated the greater his/her loss of intellectual capacity, as indicated by standard intelligence test (IQ Test). IQ has been shown to be

5 significantly higher among children whose hypothyroidism was detected and properly treated prior to 6 weeks of age versus those whose hypothyroidism went untreated for 6 to 12 weeks. For prevention or treatment of hypothyroidism, an appropriate dose of thyroid hormone must be used. Over- and under-use pose serious, lifelong consequences for the infant. Babies born without sufficient thyroid hormones need to

10 start thyroxin supplement as soon as possible after birth. One article reported that a 12-year old male patient had growth retardation (Thyroid Foundation of Canada, *Thyrobulletin*, Vol. 14, No. 1, 1993). This patient's clinical appearance, medical history and biochemical profile constituted a classic picture of hypothyroidism secondary to adolescent-onset Hashimoto's disease. Hypothyroidism is the most common

15 endocrinologic cause of growth failure in this age group. Laboratory tests showed that his T4 was less than 1 ug/dl, his T3 resin uptake was 36% and his TSH > 64 S.I. units. Elevated antithyroid antibody titers established a diagnosis of chronic lymphocytic thyroiditis - Hashimoto's disease. The patient was given a replacement regimen of 0.1 mg of levothyroxine tablet, four times a day. He quickly began to catch up on the

20 growth curve. His complexion returned to normal. This patient's repeat T4 was 8.0 ug/dl and his highly sensitive TSH (immunoradiometric assay) was 0.76 S.I. units, falling within the normal range (0.7-5.0). This case indicates that supplementation of thyroid hormone is helpful to certain people. Currently, no infant formulas contain thyroid hormones.

The aged people also have the risk of thyroid dysfunction. Hypothyroidism may be masked by clinical features, which it shares with the symptoms of aging. These include a general slowing of mental and physical function, a tendency to lower body temperatures and cold intolerance, weight gain, constipation, hardening of the arteries, elevation of serum cholesterol, elevation of blood pressure, and anemia. Those who have severe hyperthyroidism often have a dramatic improvement in mental and physical function following appropriate thymic hormone treatment. Thyroid problems may run in families. They may also be part of genetic link to diseases such as juvenile diabetes and arthritis, and to early gray hair and vitiligo (white patches on the skin). If these problems are in the close family -- parents, aunts and uncles, grandparents -- it's a good idea to watch for thyroid problems in the child. Girls are especially prone to have thyroid problems. Infants born in these families need to have thymic hormone supplement. Several prior art references propose to supplement certain forms of thymic hormones as a drug. It is obvious that for infants and for the aged people, the long-term use of a drug is not only an inconvenience, but also poses the risk of using an incorrect dose. A food containing the right concentration of thymic hormones for each age group may be used to practically achieve the goal of improved thymic hormone status, in these people.

Many antibodies present in human milk play an important role in promoting an infant's health. Rotavirus is the most common viral pathogen for causing infancy diarrhea. Rotavirus antibody is an immunoglobulin, which may be used to prevent and treat rotavirus infection. Since viral diarrhea has severe consequences for infants and lacks a therapeutic agent, it is critically needed to develop an infant formula that contains this antibody. The patent filed by Paul SM (Immunoglobulin and Fiber-Containing Composition for Human Gastrointestinal Health, April 28, 1998 U.S. Patent

No. 5,744,134) proposed to use both carbohydrates and immunoglobulins to prevent/treat gastrointestinal diseases. However, the use of an antibody against rotavirus was not included in that patent disclosure. The product described in the Paul patent needs further improvement for providing a strong health promoting effect.

5 The human colon accommodates a complex microbial ecosystem containing a large number and variety of bacteria. This community of microflora may play a major role in the health of an infant and other population sectors. Newborn infants are devoid of intestinal flora at birth. However, as a result of contact with the mother during birth and subsequent breastfeeding, the intestinal flora rapidly increases. Bifidobacteria and
10 lactobacilli are called probiotic bacteria, and they are major colonic flora in breast-fed infants. Formula-fed infants have about one-tenth to roughly the same the number of bifidobacteria and lactobacilli as breast-fed infants. Because of the potential health benefits of probiotic bacteria, it would be desirable to increase the number of these bacteria in the colon. One approach that may be used to increase the colonic
15 bifidobacteria and lactobacilli in humans is to feed them live probiotic bacteria. Certain problems may be associated with this approach. The microbes may not remain viable in their transit through the upper gastrointestinal tract to the colon. Additionally, the microbes may not be able to establish permanent colonies in the colon. A second approach is to use prebiotics, which are specific food components that selectively
20 stimulate growth and/or activity of probiotic bacteria. One group of prebiotics is fructans. Fructans are polymers of beta-D-fructosyl units having short, medium and long chains with a polymerization ratio of 3 to 9 (oligofructoses) to medium-length chains with a degree of polymerization of 10 up to about 60 (Inulin). Fructans are present in common fruits and vegetables, such as bananas. The presence of fructans
25 and its fermentation in vitro result in an increase in the number and metabolic activity of

beneficial bacteria (Wang et al, J. Appl. Bacteriol. 75:373-380, 1993; Mallet et al. in Role of the Gut Flora in Toxicity and Cancer, pp. 347-382). Furthermore, oral administration of fructans such as oligofructose and inulin has been shown to increase the number of beneficial bacteria in human stools (Gibson et al. Gastroenterol.

5 108:975-982, 1995). As a result, fructans have been recommended as supplements to adult humans' diets, and are used in certain commercial infant formulas. The most closely related prior art was described by Dohnalek et al. (Use of Indigestible Oligosaccharides to Prevent Gastrointestinal Infections and Reduce Duration of Diarrhea in Humans, October 27, 1998 U.S. Patent No. 5,827,526). In this patent, only
10 fructoligosaccharide was used to reduce diarrhea duration in infants. They did not use other health promoting factors in combination to have more effective health protection as will be used in the present invention.

Human milk contains oligosaccharides, virus antibody and hormones. Many studies have shown that human milk fed infants, as compared to those fed infant
15 formulas, have a significant advantage of having a better immune function, having a lower risk of infectious diseases, and having a higher score in standard intelligence testing ("IQ"). Although many other components in human milk and many environmental factors might also contribute to those differences, the lack of hormones, oligosaccharides, and antibodies in most of the commercial infant formulas is one of
20 the possible reasons. Hence, an infant formula supplemented with those factors is disclosed in the present invention.

The present invention is a method for the production of health promoting foods used for mammals. The food composition comprises mixtures of one or more fructans, antibodies, including rotavirus antibodies, and one or more hormones, including thymic
25 hormones. Also, the invention is to a method of fortification of foods particularly useful

in promoting infants' overall health and mental development, and in maintaining physiological function at an optimal level and combating infectious disease, memory loss, and aging in an older adult. The method includes four parts: the first part is to a new food composition in which the hormone is fortified alone, or in combination with fructans, and/or with rotavirus antibody, and all are added at an appropriate level. The second part is a food manufacture process in which the hormone and/or the antibody retains its biological activity after completion of the food processes. The third part is a method of using a stable form of hormones and/or antibodies as food ingredients. The fourth part is a method of use of the health-promoting foods supplemented with those factors.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a new method of producing a food which can enhance immunity and other body functions. Good immunity in a mammal is key for protecting its health. Thymic hormones, adrenal hormones, thyroid hormones, growth hormones, insulin-like growth hormones, sex hormones, melatonin hormone play critical roles for a human or an animal in performing many functions, especially those of immune system, neuroendocrine system, reproductive system, and the central nervous system. The present invention relates to the foods fortified with those hormones to benefit mammals. The present invention is an alternative to a drug therapy. Since these hormones are present in human milk, they can be safely added into health promoting foods, including infant formulas. Baby or infant as used herein is intended to mean a child in the first 2-years of life. The non-infant population may also consume the functional food to protect their health.

Viral diarrhea is a common health problem for many infants worldwide.

Rotavirus is the most common viral pathogen that causes severe diarrhea in human infants. The present invention is to incorporate an antibody against rotavirus into baby food. It is known that rotavirus antibody may be isolated from an egg laid by a chicken
5 immunized with a rotavirus vaccine, or from serum/milk of a cow immunized with a rotavirus vaccine. Due to the fact that eggs and cow milk are common foods for feeding an infant, the less purified rotavirus antibody from a chicken egg and/or from cow serum/milk may be directly used as an ingredient for infant formula if they otherwise meet the standards of infant formula ingredients. If the rotavirus antibody is
10 obtained from the genetic modified organism or plant (bacterium or fungus), the antibody must be highly purified before use as an ingredient to avoid any potentially harmful substances going to infant food.

The present invention is also based upon the discovery that certain fructans have the ability to selectively stimulate growth of beneficial bacteria in the colon. The
15 fructans used in the present invention are water-soluble and can be directly incorporated into a baby food composition. The term fructans herein is to mean those fructans that are naturally present in common edible food plants. The fructans have a number of properties that allow them to serve as components in a baby food composition. They are indigestible carbohydrates for the human body since humans
20 lack the digestive enzymes to hydrolyze these molecules. The fructans of the present invention serve as a preferred source of carbon and energy for beneficial bacteria in the intestinal tract, like bifidobacteria and lactobacilli. Thus, the fructans used in the present invention have a probiotic effect to selectively stimulate growth of beneficial bacteria in the colon, and to improve the intestinal immune function against infection.

This part of the food composition is used to build the body's normal defense system and thus, to protect the body's general health.

Hormone replacement therapy, or drug treatment, has a significant problem in dosing if it were used for a long time. Chronic over-supplement of thyroid hormone
5 may cause craniosynostosis - premature closure of the cranial sutures - and abnormal brain maturation. Other skeletal effects of overdosing are closure of epiphyses and possible osteoporosis. Over-treated infants are irritable, nervous and have problems gaining weight. On the other hand, chronic under-supplement retards physical and intellectual growth and possesses all of the eventual problems consistent with
10 hypothyroidism. For preventing and/or treating hypothyroidism in infants and young children, the appropriate dose should be used during the first two years of life, which is a period of exceptionally rapid growth and hormone demand. Thyroid hormones should be given as a supplement if the thyroid is chronically under-performing. This supplement must almost-always be taken throughout life. Therefore, a specially made
15 food containing thyroid hormones at an appropriate concentration is necessary and is addressed by the present invention.

The present invention is a method to fortify food with one or several hormones alone, or in combination with the other beneficial factors: fructans, which are soluble dietary fibers used to help in building the body's normal defense system; viral/bacterial
20 antibodies, which are used to effectively fight against infectious diseases, especially rotavirus caused diarrhea. The main beneficial factor here is hormone. Hormones are used to increase the overall immune function and to improve the intellectual performance of a mammal. One composition, of the present invention, is provided in Table 1 below. The composition of other health promoting foods is similar in the types
25 of nutrients but are different in the quantities of the nutrients. Fortified food, of the

present invention, is useful for promoting and protecting the health of human infants and aged people. The basic ingredients of the food to be supplemented with at least one thymic hormone, and optionally with at least one fructan and/or rotavirus antibody, may be obtained from the prior art.

Table 1

Approximate Composition of an Infant Food in a Liquid Form
(Per Liter)

5		
10	Protein, g	15.3
	Fat, g	36.5
	Carbohydrate, g	74.5
	Linolenic Acid, g	5.5
15	Vitamin A, IU	2900
	Vitamin D, IU	440
	Vitamin K, mcg	112
	Vitamin B ₁ , mg	0.5
	Vitamin B ₂ , mg	1.5
20	Vitamin B ₁₂ , mcg	3.24
	Niacin, mg	9
	Folic Acid, mcg	155
	Pantothenic Acid, mcg	4250
	Biotin, mcg	45.0
25	Vitamin C, mg	150
	Choline, mg	156
	Inositol, mg	38
	Calcium, mg	975
	Phosphorus, mg	650
30	Magnesium, mg	75
	Iron, mg	13
	Zinc, mg	8.5
	Manganese, mcg	52
	Copper, mcg	710
35	Sodium, mg	220
	Iodine, mcg	46
	Potassium, mg	840
	Chloride, mg	620
	Taurine, mg	57.5
40	Energy (Kcal)	737
	Beta Carotene, mcg	400
	Fructans, g	0.5 - 12
	Viral/bacterial Antibody, mg	Positive to 5000 mg
	Thymic Hormone, mg	Positive to 500 mg
45	Thyroid Hormone, mg	Positive to 500 mg
	Adrenal Hormone, mg	Positive to 500 mg
	Melatonin, mg	Positive to 500 mg

In order to achieve the beneficial effects of stimulation and/or maintenance of bifidobacteria and lactobacilli, an effective amount of fructans are present in the food composition of the present invention. In determining the amount of fructans needed to elicit a stimulating and/or modulating effect on bifidobacteria, calculations may be based upon amounts known to be effective in humans. Gibson et al, *Gastroenterol*, Vol. 108, pp. 975-982, 1995 has shown that 15 grams of either oligofructose or inulin per day increases the bifidobacteria count in feces. Both the daily caloric intake and fecal mass of infants are about one-fifth to one-third that of adults (*Nutrition in Infancy and Childhood*, Pipes and Trahms, Eds., Mosby, St. Louis, 1993, pp. 30-58; Gibson et al., *Gastroenterol.*, Vol.108, pp. 975-982, 1995; *Pediatric Gastroenterol.*, Silverberg, ed., Med. Exam. Pub. Co., N.Y.). Therefore, it is estimated that the effective amount of fructans per day is approximately 5 grams for human infants. Preferably the fructans should be in a concentration of between 3 to 6 grams per liter in the ready-to-feed formula.

The effective amount of rotavirus antibody in baby food is dependent on the specific activity of the ingredient, since other protein molecules may also present in the ingredient. Depending on the specific activity of the rotavirus antibody, the effective amount of this bioactive protein should be in a range of about 0.01 to 5 grams per liter in the ready-to-feed formula. The actual amount of the rotavirus antibody to be incorporated into the food should be decided after measuring the specific activity of the ingredient for each lot before the baby food is manufactured.

The effective amount of hormones is dependent on the specific activity of the ingredients. Below, thymic hormone is used as an example. The amount of thymic hormone to be added to food is dependent on the specific activity of the ingredients, since other peptide/protein molecules may also be present in the ingredient. Also,

different kinds of users may need different amounts of thymic hormone fortification in food. For infant formulas, the reliable reference of thymic hormone supplementation is the measurement of the human milk. The measurement should include the concentration of the total and individual thymic hormones in human milk. The human milk samples should be collected freshly from more than 30 randomly approachable lactating women. The concentration of thymic hormones in the other foods may be individualized to achieve the best results. Or, the fortified thymic hormones may be generalized to meet a group of people's need. Depending on the specific activity of other ingredients, the thymic hormones effective amount should be in a range of 0.001 to 500 milligrams per liter in the ready-to-feed formula. The actual amount of the thymic hormones to be incorporated into the food should be decided after measuring the specific activity of the ingredient for each lot before manufacture of the food.

The compositions of the present invention may be added to any acceptable baby food formulation. Many prior art references have shown that fructans are safe and may be used in infant foods. Rotavirus antibody and thymic hormones are already present in human milk. The requirements for ingredients containing thymic hormones and/or rotavirus antibodies in infant formula is the same as that for other protein ingredients used in infant formulas, with the additional requirement that the specific biological activity be measured. The formulations may contain all the normal ingredients for infant formulas. The added fructans do not provide measurable amount of energy and do not significantly influence the utilization rate of other nutrients. The major difference will be the increased net amount of the dry material if the liquid formula is produced. Due to the fact that those fructans are relatively short chain molecules and do not significantly increase viscosity, the formula may be used without any concern. If the powder formula is produced, the density of the energy and other

nutrients will be slightly lowered. Because infants are generally fed frequently, the small dilution of energy and nutrients of the newly invented formula will have no adverse effect on growth and development. Rather, after infants have consumed the newly invented formula, they will maintain good health for a long time and will have fewer problems related to disease, such as diarrhea. Both thymic hormones and rotavirus antibodies are relatively small in quantity and would not contribute to the overall formula density. Their presence in the formula will be negligible in changing the physical quality of the product.

The following methods may be used to incorporate the three ingredients mentioned above into a food:

1. Fructans may be added into water first and then mixed with other ingredients of the food. The fructans may also be mixed first with other carbohydrates, and then mixed with the remaining ingredients of the food during the manufacture process. If the fructan is in a dry powder form, it may also be added into a pre-mixed powder of the major ingredients of the food by using a dry blend machine. Heat treatment will not have an impact on the functionality of fructans since the soluble fiber molecules are stable under the heat treatment commonly used for food production, including the manufacture of infant formula.

2. Thymic hormones and rotavirus antibodies are not regular amino acid/peptide and/or protein molecules. Their biological activity may be significantly influenced by high heat. The first method of incorporation of these two active ingredients in a dry powder form is to mix them into other ingredients by using a dry blend machine. Many other methods may be used to mix the active ingredients into other ingredients as long as the activity of thymic hormones/rotavirus antibody is retained. The current technology makes it possible to produce a heat-acid-proteinase resistant bioactive

product. Those technologies, such as, encoding technology, micro-liposome technology, production of lyocells, and manufacture of nano-particles, are mentioned in the prior art and may be used to produce a stable form of thymic hormones and/or rotavirus antibodies. The thymic hormones and antibodies produced may be directly
5 mixed with other ingredients, and then the whole health promoting food may be treated with an ultra high temperature to prevent food spoilage, especially for the liquid formulas.

3. Production of dietary supplements. Thymic hormone, adrenal hormone (DHEA) and melatonin, are safe hormones. DHEA and melatonin have been used
10 singly as a dietary supplement for a long time. In the present invention, any combination of those hormones each at an appropriate amount, can be formulated for meeting the need of the users. Those hormones can be directly dry-blended together. And, one or more of those hormones can be mixed with fructans, and/or viral/bacterial antibody, to produce a multi-functional product. The manufacture methods have been
15 taught in the prior arts.

The method of using health-promoting food of the present invention is different slightly from other foods. For example, the liquid formula containing thymic hormones for aged people may not be boiled due to the potential fact that the active molecule(s) may be inactivated after boiling. If the health promoting food is in a powder form, the
20 water for dissolving the powder formula should be pre-boiled and cooled to a warm temperature before use. If the hormone and/or antibody in the formula are in a heat-acid-proteinase resistant form, the common method of heating the formula may be used. If the formula is in a ready-to-feed form, the user or the feeder of the infant may directly use the liquid formula without further work and it does not matter if the active
25 ingredients are heat-acid-proteinase resistant or not.

Examples

Example 1 Subject Number 1 (BZZ) is a 67-year-old female physician. She has managed to have thyroid hormone supplement added to her food for more than 16 years. The reason she started the thyroid hormone supplement was that she found, 16 years ago, that she had a lowered serum T3 and T4 but an elevated TSH level. This was accompanied with high blood pressure (160/120 mmHg) and postmenopausal syndromes (PMS). So she started to make and drink milk supplemented with thyroid hormone (3 to 10 mg per day). Three months after regularly drinking the thyroid hormone supplement, her PMS disappeared and her blood pressure changed to 120/80 mmHg. This physician has continued to ingest thyroid hormone supplement for 16 years without any side effects. At 67 years of age, she is able to do what she could do when she was 55 years old. She has had no age related skin pigmentation change. For this physician, thyroid hormone supplement seems to have slowed down the aging process.

Example 2 Subject Number 2 (PEP) is a 66-year-old male physician. When he was 54 years of age, it was found that he had a lower serum T3 and T4 but a normal TSH level. At that time, it was easy for him to catch cold and he had insomnia. Also, he was constipated. He followed the advice of an endocrinologist and started to use milk supplemented with thyroid hormone (about 5 - 10 mg per day) and had two pieces of banana a day. It took him four months to get rid of these symptoms after taking the thyroid hormone supplement. He continued to take thyroid hormone supplement for 12 years without any side effects. In recent years, he has made and consumed milk supplemented with both thyroid hormone and inulin. At 66 years of age, he seems much younger than the same aged colleagues. His constipation problem has been

eliminated. For this physician, consuming the food supplemented with thyroid hormone and fructan brings him multiple benefits.

Example 3 Subject Number 3 (XWL) is a premature female infant. Her birth weight was 1820 grams. At birth, she had a soft cry and a lower than normal body temperature. She was placed in an incubator for 30 days. The physician instructed her parents to allow her to consume thymic hormone supplemented milk. This premature infant was given thymic hormone supplemented foods for three years. Unlike other premature infants, she did not have frequent infectious illnesses during the first three years of life. Her body weight and height at three years of age was similar to others of her age. Her intellectual ability was better than most of the same aged children. During the three years of thymic hormone supplement, no side effects were observed in this child.

Example 4 Subject Number 4 (HDL) is a normal male infant. At three month of age, his body weight was in a low percentile. He already had two infectious diseases. The physician let him drink milk supplemented with thymic hormone and an immunoglobulin for one year. This infant's growth gradually sped up. By 12 months of age, his body weight was in the 60th percentile. There were no more infections during the 9-months of taking the thymic hormone fortified milk.

We Claim:

1. A method of producing a health promoting food for a mammal, said method comprises fortifying said food with a therapeutically acceptable amount of at least one immune enhancing hormone and optionally additionally fortifying said food with fructans and/or antibodies at a therapeutically acceptable level and in any combination.
2. The method of claim 1, wherein said health promoting food is an infant formula.
3. The method of claim 1, wherein said health promoting food is a nutritional product for people of any age.
4. The method of claim 1, wherein said mammal is a human.
5. The method of claim 1, wherein said mammal is an animal.
6. The method of claim 1, wherein said immune enhancing hormones are selected from the group consisting of thymic hormones, thyroid hormones, growth hormones, insulin-like growth hormones, sex hormones, melatonin hormone and adrenal hormones.
7. The method of claim 6, where in said thymic hormones are thymosin, thymulin, thymopoietin, and thymic humoral factor.
8. The method of claim 1, wherein said fructans are selected from the group consisting of oligofructoses and inulin.
9. The method of claim 1, wherein said fructans are polymers of 3 to 60 fructose units.
10. The method of claim 1, wherein said antibodies are virus antibodies.
11. The method of claim 1, wherein said health promoting food is an infant formula supplemented with thymic hormones.

12. The method of claim 1, wherein said hormones and/or antibodies are made stable for heat treatment, in acidic environment and at the presence of proteinases.
13. The method of claim 1, wherein said health promoting food is in a liquid form, semi-liquid form, concentrated liquid form, gel form, or solid form.
14. The method of claim 1, wherein said health promoting food is an infant formula used to reduce diarrhea in an infant.
15. The method of claim 1, wherein said health promoting food is a nutritional product used for slowing down the aging process.
16. A health promoting food supplement comprising a therapeutically acceptable amount of at least one immune enhancing hormone and optionally additionally comprising fructans and/or antibodies.
17. The method of claim 6, wherein said immune enhancing hormones can be delivered through a nutritional matrix to those who are in need to have any of those hormone supplements on a regular basis.
18. The method of claim 6, wherein said immune enhancing hormones can be delivered through a dietary supplement form to those who are in need to have any of those hormone supplement on a regular basis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/41080

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : 514/2, 23; 530/300, 303, 350, 399

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 23; 530/399

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, EMBASE, SCISEARCH, CAPLUS

search terms: nutritional or nutrition, insulin, hormone, infant, formula, oligofructose

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,902,617 A (PABST) 11 May 1999, see entire document	1, 2, 11, 14
Y	ROBERFROID, M. Concepts in Functional Foods: The Case of Insulin and Oligofructose. J. Nutr. 1999, Vol. 129, pages 1398S-1401S, see entire document.	1-18
Y	KOK et al. Insulin, Glucagon-like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide and Insulin-like Growth Factor I as Putative Mediators of the Hypolipidemic Effect of Oligofructose in Rats. J. Nutr. Vol. 1998, Vol. 128, pages 1099-1103, see entire document, especially page 1101-1102.	1-18

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:		"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

27 SEPTEMBER 2001

Date of mailing of the international search report

30 OCT 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer:
ANISH GUPTA

Telephone No. (703)-308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/41080

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GIBSON, R. Dietary Modulation of the Human Gut Microflora Using the Prebiotics Oligofructose and Insulin. J. Nutr. 1999, Vol. 129, pages 1438S-1441S, see entire document.	1-18
Y	US 5,906,833 A (KLATZ) 25 May 1999, see entire document.	1
----- A		----- 2-18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/41080

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

A61K 31/70, 38/18, 38/22, 38/28, 38/30; C07K 14/475, 14/60, 14/61, 14/62, 14/65